REMARKS

Claims 1-27 are currently pending in this application. No new matter has been introduced into this application. In view of the amendment and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims.

I. The Tables in the Specification have been Amended

Tables 1-6 have each been amended from single-line spacing to 1½ -line spacing in compliance with 37 C.F.R. §§ 1.52 and 1.58. Applicants have not added, deleted, or substituted any residues of any sequence listing in Tables 1-6. Any discrepancies between the sequence listings in Tables 1-6 in this amendment and the sequence listings in the application as originally filed are merely typographical, and the application as filed will control. Applicants respectfully request that the objections to the tables be withdrawn.

II. The Rejections under 35 U.S.C. § 103(a) have been Overcome

Claims 1-27 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Ancellin & Hla, 1999, *J. Biol. Chem.* 274:18997-19002 ("Ancellin") in view of any two or more of the following: Conway *et al.*, 2000, *J. Biol. Chem.* 275:20602-20609 ("Conway"); Schioth *et al.*, 1998, *Mol. Pharm.* 54:154-161 ("Schioth"); Wu *et al.*, 1997, *J. Biol. Chem.* 272:9037-9042 ("Wu"); Meng *et al.*, 1996, *Eur. J. Pharm.* 311:285-292 ("Meng"); Holtmann *et al.*, 1995, *J. Biol. Chem.* 270:14394-14398 ("Holtman"); Takagi *et al.*, 1995, *J. Biol. Chem.* 270:10072-10078 ("Takagi"); Buggy *et al.*, 1995, *J. Biol. Chem.* 270:7474-7478 ("Buggy"); Kim & Devreotes, 1994, *J. Biol. Chem.* 269:28724-2873 1 ("Kim"); Gether *et al.*, 1993, *J.*

Biol. Chem. 268:7893-7898 ("Geethar"); and Kobilka *et al.*, 1988, *Science* 240:1310-1316 ("Kobilka").

According to the allegations in the Office Action, it would have been *prima facia* obvious to one of ordinary skill in the art after reading the disclosure of Ancellin in view of two or more of the cited references to have constructed a series of chimeric Edg receptors composed of various combinations of transmembrane, intracellular, and extracellular domains from Edg-1 and Edg-3 for the purpose of identifying those structural domains in each of those two related receptors that are responsible for the specific pharmacological properties of the receptor. *See* September 26, 2003 Office Action at pages 3-4. Applicants respectfully traverse this rejection for the reasons set forth herein.

Applicants respectfully submit that the Examiner has failed to establish the legally required *prima facie* case of obviousness based on the disclosure of Ancellin in combination with Conway, Schioth, Wu, Meng, Holtmann, Takagi, Buggy, Kim, Gether, and Kobilka. The combination of references fails to suggest the claimed invention and fails to motivate one of ordinary skill in the art to modify the teachings of the references to produce the claimed invention. Specifically, the cited references alone or in any combination fail to provide the legally required suggestion of a chimeric Edg receptor, wherein an extracellular domain and transmembrane domain of a first G protein-coupled receptor ("GPCR") is linked to a chimeric intracellular domain comprising an intracellular strand of a second GPRC. In fact, the chimeras disclosed in the cited references comprise structural substitutions to an GPCR that have no relation to, are completely irrelevant, or teach away from the chimeric receptor recited by the pending claims.

For the Examiner's convenience, claim 1 is reprinted below:

1. A chimeric Edg receptor comprising:
a) an **extracellular domain of a first Edg receptor**;
b) a **transmembrane domain of the first Edg receptor**, wherein the transmembrane domain is operably linked to the extracellular domain; and
c) a chimeric intracellular domain comprising **an intracellular strand of a second Edg receptor**, wherein the chimeric intracellular domain is operably linked to the transmembrane domain.

Ancellin, the primary reference, discloses coupling of Edg receptors to a Gαq protein; Ancellin does not teach or suggest substitution of any portion of an Edg receptor, (*e.g.*, an intracellular strand), as recited by the pending claims. Moreover, each of Conway, Schioth, Wu, Meng, Holtmann, Takagi, Buggy, Kim, Gether, and Kobilka merely discloses a completely different and unrelated variety of chimeric G-protein-coupled receptors ("GPCRs").[1]

The Examiner cites various sections of each of the cited secondary references to illustrate chimeric receptors. *See* Office Action at page 5. However, not one of the cited references suggests chimeras in an Edg receptor, nor do the references disclose specific intracellular domain chimeras as recited by the claimed invention. Applicants do not contradict that each of the secondary references indeed discloses a chimeric receptor; however, Applicants respectfully submit that the combination of the references fails to disclose the claimed chimeric Edg receptors of the invention or to motivate one of ordinary skill in the art the modify the teachings of the references to produce the claimed chimeric Edg receptors.

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1 Applicants respectfully point out that in contrast to the Examiner's assertion that they are attacking the references individually to show non-obviousness, they are in fact demonstrating that the references fail to provide the requisite suggestion of the claimed invention and further fail to motivate one of ordinary skill in the art to modify the references to achieve the claimed invention.

In particular, Conway discloses chimeras of human melatonin mtl receptor and melatonin-related receptor used to assess melatonin-binding and ability to increase cAMP in cells. Schioth discloses chimeras of melanocortin MC1 and MC3 receptors assessed for ligand binding and ability to increase cAMP in cells. Wu discloses human cholecystokinin ("CCK") receptor chimeras of CCK-AR and CCK-BR subtypes constructed to determine the structural basis of CCK-AR functionally coupled to G_{5j} a G protein that stimulates adenylyl cyclase leading to cAMP production. Meng discloses chimeras of the S-, *K*-, and μ-opioid receptors that are assessed for opioid ligand selectivity. Holtmann discloses chimeras of a secretin receptor and a vasoactive intestinal polypeptide (VIP) receptor assessed for cAMP response and ligand binding. Takagi discloses chimeras of the human endothelin type A and type B receptors. Buggy discloses chimeras of the human glucagon receptor and human islet GLP-I receptor each assessed for glucagon binding. Kim discloses CAMP chemoattractant receptor chimeras composed of the cARl and cAR2 subtypes that were analyzed for cAMP binding. Gether discloses chimeric NK_l and NK3 receptors that are assessed for peptide agonist selectivity. Kobilka discloses chimeric adrenergic receptors in which portions of the a_2 and 0 2 adrenergic receptors have been substituted.

Despite the twelve references cited by the Patent Office to provide a suggestion of obviousness, Applicants respectfully submit that the chimeric receptors disclosed in the cited references simply provide no teaching, no suggestion, and indeed no motivation to one of ordinary skill in the art to select the elements from the cited references for combination in the manner claimed by Applicants in any of the claims.

Moreover, the Examiner states on page 5 of the Office Action, "[i]f one ignores the 'Edg' limitation of claim 1, it encompasses a chimeric G protein coupled receptor comprising

at least one extracellular and transmembrane domain from a first receptor and at least one intracellular domain from a second receptor." Applicants respectfully submit that if the Examiner ignores any limitation of any claim, this is a legally improper analysis for determining obviousness. In particular, as the Examiner is aware, it is the invention as a whole that must be considered in obviousness considerations. *Hartness International, Inc. v. Simplimatic Engineering Co.*, 819 F.2d 1100 (Fed. Cir. 1987). And, not one of the GPCRs recited by the references is an Edg receptor as recited by claims.

Thus, even assuming *arguendo* one of ordinary skill in the art were motivated to combine Ancellin with all of the references cited by the Patent Office, the combination nonetheless fails to produce the claimed invention. The combination clearly does not suggest a chimeric Edg receptor comprising the extracellular and transmembrane domains of a first Edg receptor and a chimeric intracellular domain comprising an intracellular strand of a second Edg receptor, wherein the chimeric intracellular domain is operably linked to the transmembrane domain, as recited by the pending claims. Applicants respectfully submit that only with the aid of impermissible hindsight could the chimeric receptor recited by the pending claims be extracted from the collection of art cited in the office action. And as the Examiner is aware, it is improper to use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988).

Because none of the references teach or suggest a chimeric receptor wherein the extracellular domain and transmembrane domain of a first GPCR is linked to a chimeric intracellular domain comprising an intracellular strand of a second GPRC, the Examiner is requested to withdraw this rejection.

Finally, Applicants point out that the Examiner correctly stated, "the particular embodiments of the invention identified as 'Edg 1/3(i3ct),' 'Edg 1/3(i2i3ct),' and 'Edg 5/3(i3ct)' are free of the prior art." *See* Office Action at page 6. On closer inspection Applicants believe that the Examiner will ascertain that independent claim 13, which includes the above-identified embodiments is also patentable in its entirety.

III. Conclusion

Respectfully, Applicants submit that the claims in the application are clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17, which may be required, to our Deposit Account No. 50-0310.

The Examiner is invited to telephone the undersigned should he find that an interview or further discussion might advance the examination of this application.

Respectfully submitted

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